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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,968	06/01/2001	Jack R. Wands	21486-047	3051

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,968	WANDS ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-26 and 50-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-26 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election without traverse of group II, filed September 30, 2002 is acknowledged. The preliminary amendment filed September 30, 2002 in paper no. 12 has been entered. Claims 20-26 and 50-52 are pending.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-26 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rats which have been administered directly into their brain an exogenous DNA sequence encoding AD7c-NTP operatively linked to a promoter in association with a histone and a liposome, wherein expression of said DNA sequence in neuronal cells of the rat results in neuronal cell death, and methods of using these rats in methods of assay to determine compounds which decrease neuronal cell death, inhibit the expression of APP and inhibits the production of plaques in the brains of the rats does not reasonably provide enablement for any non-transgenic model for Alzheimer's disease and methods of using the models. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to non-transgenic animal model for Alzheimer's disease comprising a nonhuman animal, wherein the animal comprises an exogenous AD7c-NTP, and methods of using the animal. The claims are unpredictable because the delivery of DNA sequences across the blood brain barrier was inefficient to cause sufficient expression of the AD7c-NTP DNA sequence to obtain an AD phenotype, and primate were known in the art not to be responsive to the presence of amyloid core proteins.

Games reports that the infusion of β-amyloid into the hippocampus of rats did not result in the formation of any amyloid relate toxicity or pathology (abstract). Podlisny discloses that the injection of amyloid β into monkey cortex did not result in the formation of specific cellular changes associated with Alzheimer's pathology (abstract). Although AD7c-NTP and amyloid-β are unrelated protein in structure, both proteins cause neuronal death in Alzheimer's disease. Thus, it is unpredictable that administration of AD7c-NTP into nonhuman primate brains would result in the formation of an Alzheimer's disease related pathology, and thus that the primate would not be useful in as a model for Alzheimer's disease. It is noted that Games was unsuccessful with rat, but applicant was successful in making a rat expressing exogenously injected DNA sequence encoding AD7c-NTP. It is not possible for the examiner to determine if the use of a vehicle, such as a liposome and histone complex was essential to making the claimed model. however, Nishimura states that adenovirus alone would not cross the blood brain barrier until the adenovirus was in a hypotonic solution (page 2394, col. 2, lines 10-20). Furthermore, although the issue is more directed to gene therapy, Wolff states that efficient transfer of DNA and the stable expression of transgenes is a challenging problem (col. 1, lines 19-22). Wolff discloses the use of an amphipathic compounds and DNA binding proteins to facilitate introduction of DNA into cells sufficiently to achieve a desire effect (col. 2, line 1-5). Claim 26 states that AD7c-NTP is expressed in vascular endothelial cells. However, this is not enabled as the specification provides no guidance on delivering the DNA sequence encoding AD7c-NTP to vascular endothelial so that expression of the DNA sequence results in a phenotype associated with Alzheimer's disease. Therefore, and for these reasons, the claims as written lack enablement because of art recognized unpredictabilities in obtaining DNA expression sufficient to cause the formation of an Alzheimer's disease pathology in the breadth of

nonhuman animals, and primates, or such expression without the use of a carrier for the DNA sequence encoding AD7c-NTP.

Thus, at the time of the present invention, the skilled artisan would have needed to engage in an undue amount of experimentation to implement the claims without a predictable degree of success.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-25 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishimura et al (1998) J. Neurosci. 18, pages 2387-2398 in view of de la Monte et al (1997) J. Clin. Invest. 100, pages 3093-34104.

Nishimura teaches the degeneration of neurons in the hippocampus of rats injected steriotaxtically with an adenoviral vector comprising a DNA sequence encoding APP 695 (). The adenovirus in a hypotonic mannitol buffer was injected into the hippocampus, and expression was detected at 4 days post injection (page 2392, figure 4). Degenerating neurons were found in the intrahippocampal regions (page 2389, col. 2, parag. 1, lines 21-25). Nishimura further states that APP immunoreactive materials were accumulated with degenerating neurons (page 2388, col. 1, lines 3-4).

de la Monte teaches that an Alu sequence-containing cDNA, AD7c-NTP, over expressed in Alzheimer's disease brains (abstract and page 3094, col.1, lines 11-13). Post-mortem studies showed that AD7c-NTP was present in higher levels in AD brains than in aged control brains (page 3102, col. 1, parag. 1, line 1 to col. 2, line 1). Further, de la

Monte teaches that the over expression of a DNA sequence encoding AD7c-NTP in neuronal cells promotes neuritic sprouting and cell death, two principal pathological processes in AD neurodegeneration (page 3102-3103, bridg. sent.).

Thus, it would have been obvious to the ordinary artisan to administer an adenovirus vector as taught by Nishimura, where a DNA sequence encoding AD7c-NTP, as taught by de la Monte, had been substituted for a DNA sequence encoding APP 695, injecting the adenovirus into the hippocamal region of a rat's brain to observe the effects of AD7c-NTP over expression. Motivation is given by both Nishimura and de la Monte. Nishimura states that the over expression of APP 695 resulted in neuronal degradation in situ, and de la Monte states that over expression of AD7c-NTP in neuronal cells in culture resulted in death of the cells. Further, at the time of filing, it would have also been obvious to the ordinary artisan to use the rats to determine compounds that enhanced neuronal cell viability, decreased APP expression or decreased plaque formation. Thus, a reasonable expectation of success would be provided by the combined references of Nishimura and de la Monte at the time of filing.

As for the limitation that the animal expresses an exogenous Ad7c-NTP polypeptide in a neuronal cell for at least 48 hours, it is taken that the expression found at 5 days indicates expression for at least 48 hours. The PTO has no means to perform such tests, and thus applicant must argue or provide evidence that the expression demonstrated in the prior art was not at least for 48 hours.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the

claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
November 14, 2002